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Dedicated to B.I. Buzykin on His 80th Anniversary

Reactions of Unsaturated Ketones with Bis(trimethylsilyl) Hypophosphite

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Abstract—Bis(trimethylsilyl) hypophosphite reacts with unsaturated ketones (methyl vinyl ketone and mesityl oxide) to give, depending on the reaction conditions, 1 : 1 or 1 : 2 adducts after hydrolysis. It was found that the intramolecular cyclization of the 1 : 2 reaction product with mesityl oxide, trimethylsilyl bis(2-methyl-4-oxopentan-2-yl)phosphinate, yields, after hydrolysis, a phosphorinane with exocyclic carbonyl and hydroxyl groups.

Keywords: bis(trimethylsilyl) hypophosphite, mesityl oxide, methyl vinyl ketone, bis(3-oxobutyl)phosphinic acid, phosphorinane

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Phosphonates attract special interest among organophosphorus compounds due to their broad-spectrum biological activity [1]. Thus, the drug Dimephosphon [2-(dimethoxyphosphoryl)-2-methylpentan-4-one], a γ-oxoalkylphosphonate, is widely applied for the treatment of acidosis, brain circulation disorders, and respiratory diseases, both as a monotherapeutic agent and in combination with other drugs [2, 3]. Hence, synthesis of new analogs and derivatives of dimephosphon is a topical and future-oriented issue.

We recently showed that pyridinoylhydrazones derived from dimephosphon and its P–C analogs act as antitubercular agents with activity comparable to isoniazid but 13 times less toxic [4].

In the present work, aimed at synthesizing new structural analogs of dimephosphon—bis(γ-oxoalkyl)-phosphinates, we have studied the reactions of bis(trimethylsilyl) hypophosphite with usaturated ketones: methyl vinyl ketone and mesityl oxide. The use of the readily accessible hypophosphorous acid and its derivatives in the synthesis of phosphonates and phosphinates is first of all explained by the high reactivity of hypophosphites and possibility to form two P–C bond in a one-pot synthesis. As known, bis(trimethylsilyl) hypophosphite **1** exhibits the highest reactivity and thermal stability among hypophosphites [5]. The reaction of hypophosphite **1** (prepared from ammonium hypophosphite and HMDS at room temperature) with methyl vinyl ketone was performed by the procedure in [6]: dichloromethane and 1 equiv of methyl vinyl ketone were added one after the other to hypophosphite **1** under argon; the mixture was stirred for 1 h, after which 1 equiv of HMDS and 1 equiv of methyl vinyl ketone were added one after the other. The reaction mixture was stirred under argon for 12 h and then hydrolyzed. Recrystallization from acetone gave 80% of bis(3-oxobutyl)phophinic acid **2a** as a light brown powder (Scheme 1).

The ^{31}P NMR spectrum of compound **2a** contains a signal at δ_P 56.8 ppm. In the ^{1}H NMR spectrum, the methylene proton signals appear as broadened doubled triplets (H^2, 1.95 ppm, $^2J_{PH}$ = 13.4, $^3J_{HH}$ = 7.7; H^3, 2.74 ppm, $^3J_{PH}$ = 11.4, $^3J_{HH}$ = 7.7 Hz). The methyl group gives a singlet at 2.17 ppm. The characteristic feature of the IR spectrum is the presence of a strong carbonyl absorption band at 1694 cm^{-1}.

The reaction with mesityl oxide by the same procedure at room temperature gave no other products